

漸進對稱性紅斑角皮症

— 病例報告 —

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Progressive Symmetric Erythrokeratoderma

— A Case Report —

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Progressive symmetric erythrokeratoderma (PSEK) is a rare disorder of cornification characterized by epidermal hyperproliferation and is inherited as an autosomal dominant trait with variable penetrance. However, it has been reported that sporadic mutations comprise of 40 percent of all cases. Patients with PSEK usually respond to oral retinoid or etretinate therapy. We report a case of progressive symmetric erythrokeratoderma that was recalcitrant to oral acitretin and topical steroid, urea and tretinoin, as well as calcipotriol. (*Dermatol Sinica* 21 : 175-179, 2003)

Key words: Progressive symmetric erythrokeratoderma

漸進對稱性紅斑角皮症是一個罕見的表皮增生化疾病，一般它屬於顯性遺傳並有不同臨床表現，但有40%的病人為偶發突變的。通常口服A酸對漸進對稱性紅斑角皮症的治療效果良好。我們報告一個漸進對稱性紅斑角皮症病例，但此病人對口服A酸，外用類固醇、尿素、A酸及維生素D衍生物等治療，效果都不彰。(中華皮誌21 : 175-179, 2003)

INTRODUCTION

The erythrokeratodermias are a group of rare hereditary cornification disorders characterized by varying degrees of erythema and hyperkeratosis. The original description of progressive symmetric erythrokeratoderma

(PSEK; OMIM 602036), by Darier in 1911, entitled "Erythrokeratodermie Verruqueuse en Nappes, Symmetrique et Progressive", but the name by which the condition is now known was given by Gottron in 1922.^{1,2} PSEK is inherited as an autosomal dominant trait. However, spo-

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radic mutations make up about 40 percent of all cases.³ We report the clinical and histologic features of a patient with PSEK.

CASE REPORT

A 23-year-old man presented with a non-pruritic rash on palms, soles, antecubital fossae, popliteal fossae and buttocks since he was one year of age. The lesions were persistent, nonmigratory, and apparently aggravated by heat and sweating. Similar cutaneous findings were present in this patient's elder sister (Fig. 1).

On physical examination, there were symmetric, hyperkeratotic, and erythematous plaques with well-demarcated margins over the palms, dorsa of both hands, wrists, feet, antecubital fossae, popliteal fossae and buttocks (Fig. 2). Skin biopsy was performed on a representative lesion from the right wrist. Histology showed orthokeratotic hyperkeratosis, retained nuclei in the cornified cells, acanthosis of the epidermis, and thickening of the granular layer. A very sparse superficial perivascular lymphocytic infiltration was found (Fig. 3). According to the clinical presentation and histological findings, PSEK was diagnosed.

The patient was treated initially with oral

acitretin (Neotigason®) 20 mg per day for 4 months, but the response was limited. In the meanwhile, the patient had an adverse effect of hair loss. Therefore, acitretin was stopped, then the patient was started on topical steroid, urea, tretinoin and calcipotriol therapy. However, the skin lesions did not improve on the topical therapy.

DISCUSSION

PSEK is clinically characterized by well-demarcated erythematous and hyperkeratotic plaques that are distributed with an almost perfect symmetry on the head, extremities and buttocks.³ The chest and abdomen are usually not involved or only have minimal involvements. These lesions usually affect the palms and soles; they appear during the first year of life or shortly thereafter. They progress during the first to second years then remain stationary, but the lesions may partially regress after puberty.³ There is no sexual predilection. Patients are otherwise mentally and physically unaffected. Although PSEK is inherited as an autosomal dominant trait, it has been reported that sporadic mutations comprise of 40 percent of all cases.³ Due to incomplete penetrance and vari-

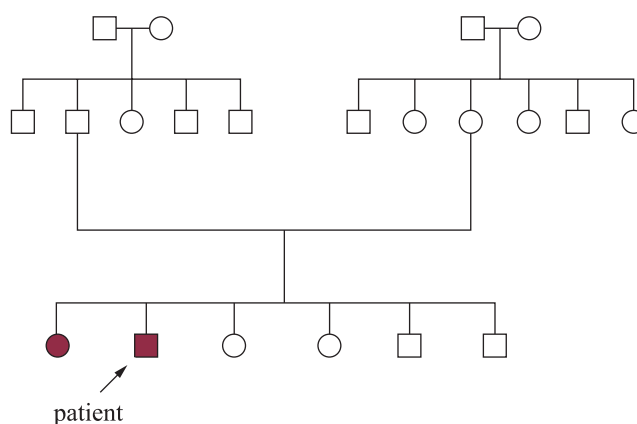


Fig. 1

Family tree of our patient

(Elder sister * was diagnosed by a dermatologist in Taichung. The condition of other family members was based on information obtained from the patient)



Fig. 2
Erythematous and hyperkeratotic plaques distributed symmetrically on palms (a), feet (b), antecubital fossa (c) and popliteal fossae (d).

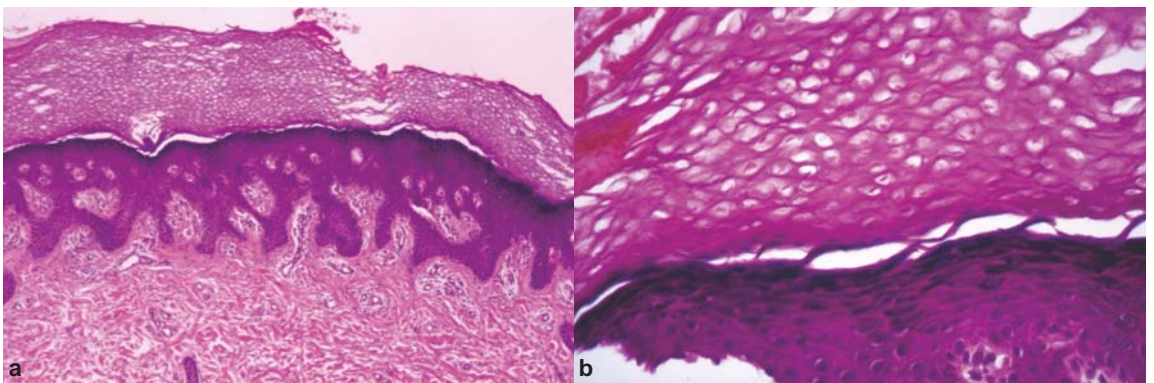


Fig. 3
A. Orthokeratotic hyperkeratosis, focal parakeratosis, acanthosis and hypergranulosis of the epidermis, and sparse superficial perivascular lymphocytic infiltration were noted, H & E stain x100 (a); few retained nuclei in the cornified cells, H & E stain x400 (b).

able expressivity of the responsible gene, not all family members of PSEK pedigree show clinical features of PSEK.³ This might explain that neither of our patient's parents had the clinical presentation of PSEK.

Histopathologically, PSEK is typified by orthokeratosis with focal parakeratosis, a well-preserved granular layer, psoriasiform hyperplasia without thinned suprapapillary plates, and a perivascular infiltrate of lymphocytes in the upper part of the dermis.^{4,5} However, the histopathology of some reported PSEK cases showed only orthokeratosis.^{6,7} PSEK should be a clinical diagnosis, since the microscopic features are nonspecific.⁷ Therefore, our patient was diagnosed with PSEK based on clinical and histological findings.

Clinical differential diagnoses include erythrodermatitis variabilis (EKV) and pityriasis rubra pilaris (PRP). EKV is well noted for its transient erythematous patches that either fade or migrate and are separated from or superimposed on more persistent polycyclic hyperkeratotic plaques on the face, extremities and buttocks. However, it was postulated that PSEK and EKV are different manifestations of the same inherited condition after 2 siblings were found to have PSEK and EKV, respectively.⁶ PRP is characterized by reddish-orange, scaling plaques and keratotic follicular papules on the head, trunk and extremities. Redness and thickening of the stratum corneum of the palms are also noted. Histology of PRP is characterized by follicular plugging.

The genetic defects underlying the erythrodermatitis are still largely unknown. We know that the cornified cell envelope (CE) is a tough structure formed beneath the plasma membrane of terminally differentiated keratinocytes. In adult human epidermis, loricrin is diffusely distributed within the cell envelope of the superficial granular cells and constitutes about 70% of the mass of CEs. Ishida-Yamamoto *et al.* speculated that in the cornified cells of PSEK, loricrin was aggregated in the nucleus and cell envelopes only have minimal loricrin labeling by immunoelectron

microscopy.⁷ Sequencing of the loricrin gene on chromosome 1q21 disclosed a heterozygous frame shift mutation, an insertion of a C nucleotide (709insC), in the patients with PSEK.^{8,9} This creates 91 missense amino acids. The entire wild-type loricrin polypeptide is 315 amino acids in length, so this mutation effectively replaced the carboxy-terminal one-third of loricrin with missense amino acids and removed approximately one-third of the glutamine and lysine residues involved in isodipeptide cross-link formation.⁹ Since loricrin is expressed widely in the epidermis covering the entire body surface and the characteristic histological and immunohistochemical abnormalities are also noted in the uninvolved skin, it is curious that the skin lesions are rather confined to certain sites. Conceivably there might be some redundancy in the structure of CE or other CE precursor proteins might be compensating for the abnormal loricrin in uninvolved areas. Otherwise, because loricrin-knockout mice showed transient erythroderma but not hyperkeratosis. Therefore it is not fully understood how the expression of gene defects is related to clinical and histopathologic phenotypes.⁸⁻¹⁰

Some studies revealed that oral retinoid or etretinate therapy for PSEK was effective, while others reported PUVA therapy was equally effective.^{11,12} Retinoid therapy was effective for PSEK because retinoid possibly suppressed the expression of both wild-type and mutant loricrin in the presence of an apparent redundancy of CE precursor protein. Tamayo and Ruiz-Maldonado treated five PSEK patients with a high dose of etretinate (1.0-1.5 mg/kg daily), and patients subsequently showed significant clinical improvements.^{11,5} However, our patient was treated with low dose of acitretin (20 mg per day) which may explain for his limited response. We were unable to adjust the dosage of acitretin to a higher level because our patient could not tolerate the side effects. Subsequently, topical tretinoin cream and calcipotriol cream were prescribed for 3 months respectively without any relief.^{7,13}

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